Individualizing Anti-Inflammatory Medications for Adults with Axial Spondyloarthritis: A series of N- of 1 trials

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AxSpA-N1-NSAIDs

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Principal Investigator
Mark Hwang, MD

Collaborators
John Reveille, MD
Charles Green, PhD
Jon Tyson, MD
Joyce Samuel, MD
Shervin Assassi, MD

Study Coordinator
Reyna Chavez
Benjamin Naovarat

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1. BACKGROUND AND RATIONALE

Ankylosing spondylitis (AS) is a disease characterized by chronic, inflammatory back pain and radiographic disease of the axial spine with an estimated prevalence of 0.2 to 0.5% in the United States population (1, 2). AS is now recognized an important subset of the broader and more prevalent diagnosis of axial spondyloarthritis (AxSpA) that is estimated to be up to 1.4% of the adult population, similar to the rheumatoid arthritis (RA) prevalence. This new definition of this disease has led to earlier diagnosis, with MRI imaging identifying a *different phenotype of AxSpA patients with disease that do not develop AS* (3). In contrast to other inflammatory rheumatic diseases, including RA, the therapeutic options for AxSpA are limited and confined to nonsteroidal anti-inflammatory drugs (NSAIDs) and, if this treatment fails, to biologic medications such as tumor necrosis factor and interleukin-17a blockers

1.1. General Introduction

Current consensus guidelines from major rheumatology professional organizations including the American College of Rheumatology/ Spondyloarthritis Association of America/ Spondyloarthritis Research and Treatment Network (SPARTAN) and the European League against Rheumatism (EULAR) recommend NSAIDs (as a class) as the first-line drug treatment for patients with symptomatic disease in AxSpA(7-9). Furthermore, the same guideline statements have suggested *continuous over on-demand* NSAID treatment for active AxSpA. Opioid medications are strongly discouraged as they do not effectively treat AS/AxSpA. US claims databases however show a 27.3-76.7% prevalence of chronic opioid use among AxSpA patients(10).

1.2. Rationale and justification for the Study

In the past, phenylbutazone (FDA-approved in 1946) was considered the NSAID of choice for the treatment of AS, but it was supplanted by NSAIDs without similar risk of bone marrow suppression. Indomethacin was then favored as an effective NSAID in AS patients, despite the lack of randomized controlled trials (RCTs) demonstrating superior efficacy(11). More recently, cyclooxygenase-2 (COX-2) selective inhibitors, such as celecoxib and etoricoxib, have shown similar efficacy in AS to non-selective NSAIDs(12, 13). At this time, 11 NSAIDs are approved for the treatment of AS in Europe and 5 in the United States; additional NSAIDs are approved for other indications and are available for use. The question that naturally arises when there are many treatment options is whether any specific NSAID is more effective as well as if the benefits of pharmacologic treatment justify the potential short and long-term associated hazards.

While recent Bayesian network meta-analysis have suggested that etoricoxib may be superior compared to other NSAIDs in terms of Visual Analog Scale (VAS) pain reduction in pairwise comparisons (14), it remains unanswered if any NSAID is superior in terms of overall disease activity that also includes important disease domains such as stiffness, fatigue, peripheral arthritis/enthesitis(inflammation of the ligamentous/tendinous attachments) in addition to spinal pain. Furthermore, etoricoxib is not FDA-approved for any indication due to cardiovascular safety concerns. It remains unknown thus if one NSAID therapy is superior to others in the clinical care of AxSpA patients.

2. HYPOTHESIS, OBJECTIVES, and OUTCOME MEASURES

2.1. Hypothesis and Objectives

Aim 1: To compare selective (COX-2) and nonselective COX inhibitors with respect to the extent to which disease activity (as assessed by ASDAS) is improved without self-reported, unacceptable side effects among individual patients with AxSpA through n-of-1 series of trials.
Hypothesis. Compared to nonselective COX inhibitors (naproxen and meloxicam), celecoxib will be the preferred medication based on short term responses for a majority (>50%) of patients.

SubAim 1A: To assess the effort required for the n-of-1 trials, the acceptability, and proportion of patients who complete the n-of-1 trials.
Hypothesis: Patients complete the n-of-1 trial will demonstrate >80% acceptability and completion of this N-of-1 trial.

Aim 2. To compare selective (COX-2) and nonselective COX inhibitors impact on Health-related Quality of Life (HrQOL) as assessed through standard gamble (SG) utility assessment and how this relates to changes in disease activity.
Hypothesis: COX-2 NSAIDS will result in higher utilities, which will strongly correlate with changes in ASDAS scores.

Aim 3: To conduct proteomic assessment of predictive biomarkers of NSAID response.
Hypothesis: Patients will demonstrate candidate serum biomarkers predictive of disease remission due to NSAID use (response = *ASDAS <1.3* on any NSAIDs treatment)

We expect at the end of these experiments, we will potentially be able to understand the differences in individual NSAID on disease activity, HrQoL as well as generate preliminary data that will identify patients more likely to respond to NSAIDs treatment *a priori.* This may allow us to change the current paradigm in AS pharmacotherapy by individualizing NSAIDs usage, decreasing opioid usage and improving health outcomes for AxSpA patients.

2.2. Outcome Measures

a. Primary Outcome Measure(s)

The primary outcome of this study will be the Ankylosing Spondylitis Disease Activity Score (ASDAS). Please see Trial Schedule for time point assessment.

b. Secondary Outcome Measure(s)

Secondary outcomes include the Standard Gamble, Patient-Information Measurement Information System (PROMIS-29), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Metrology Index (BASMI), Visual Analog Scale-Pain (VAS-Pain), Visual Analog Scale-Global VAS-Global.

STUDY POPULATION

Adults >18 years of age who fulfill ASAS classification criteria fox AxSpA and/or modified New York classification criteria for AS(22, 23) with active disease, defined as ASDAS ≥ 2.1 (24) to capture the spectrum of patients with this disease. Patients who are anticipated

to undergo biologic medication initiation/switching during the trial period (concurrent, stable biologic medication use is acceptable) will be excluded.

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Inclusion Criteria:

1. Patients must meet modified New York Classification and/or Assessment of Spondyloarthritis International Society (ASAS) criteria for Classification Criteria for AxSpA
   Ankylosing Spondylitis Disease Activity Score ≥ 2.1 **or taking continuous NSAIDs (defined as an NSAID equivalence score of >=50% over the past 6 months).**

Exclusion Criteria:

1. Changing background biologic/disease modifying-rheumatic medications within < 3 months.
2. Opioid medication use
3. Current or expected pregnancy
4. History of cardiovascular disease (previous stroke, myocardial infarction, or percutaneous intervention.
5. End stage liver disease
6. Chronic Kidney Disease > Stage IIIb

3. TRIAL SCHEDULE

	Baseline Visit (Week 1)	Visit 1 (Week 5)	Visit 2 (Week 9)	Visit 3 (Week 13)	Visit 4 (Week 17)	Visit 5 (Week 21)	Visit 6* (Week 25)	Visit 7* (Week 29)
Informed Consent	Yes	No	no	no	no	no	no	no
Medical History	yes	yes	yes	yes	yes	yes	yes	yes
Physical Exam	yes	yes	yes	yes	yes	yes	yes	yes
ASDAS	yes	yes	yes	yes	yes	yes	yes	yes
Standard Gamble	yes	yes	yes	yes	yes	yes	yes	yes
PROMIS-29	yes	yes	yes	yes	yes	yes	yes	yes
BASFI	yes	yes	yes	yes	yes	yes	yes	yes
BASDAI	yes	yes	yes	yes	yes	yes	yes	yes
BASMI	yes	yes	yes	yes	yes	yes	yes	yes
VAS-Pain	yes	yes	yes	yes	yes	yes	yes	yes
VAS-Global	yes	yes	yes	yes	yes	yes	yes	yes
LAB: Complete Blood Count (5 cc)	yes	no	no	no	no	no	no	no
LAB: C-Reactive Protein (5 cc)	yes	yes	yes	yes	yes	yes	yes	yes
LAB: Complete Metabolic Panel (5 cc)	yes	no	no	no	no	no	no	no
Baseline Serum Blood Draw (10 cc)	Yes	no	no	no	no	no	no	no
Medication Given	yes	yes	yes	yes	yes	no	yes	no
Adverse Events	yes	yes	yes	yes	yes	yes	yes	yes
Concomittant Medication Screen	yes	yes	yes	yes	yes	yes	yes	yes

*Each consecutive visit will be 4 weeks apart starting at Baseline visit (Week 1), Visit 1 (week 5) and continuing in this pattern.

4. STUDY DESIGN

Allocation will occur through REDCap with each participant randomized to a different initial drug sequence (6 possibilities: ABC, ACB, BAC, BCA, CBA, CAB) of the following three drugs: Naproxen 500 mg tablets twice daily (BID), Meloxicam 7.5 mg tablets BID and Celecoxib 200 mg capsules BID. Patients will be randomized in blocks of 6 to ensure that no drug is assigned to be the first drug tested more often than the others. Medications will be obtained by the investigation team, and then all 3 medications will be over-encapsulated in identical opaque capsules. 4 weeks worth of medication will be given out in barcoded, plastic bottles at each monthly visit to ensure double blinding to both patients and researchers.

Baseline disease activity is defined as ASDAS-CRP scores (Figure 1) with a one-week washout period off of pharmacotherapy. Treatments will be prescribed at random order through REDCAP randomization at full-dose without washout periods to maximize patient comfort and acceptability and avoid increasing disease actively, Moreover, residual effects will likely no longer be present by the end of the 4th week on the next medication when ASDAS and direct utility assessment (Study 2) are assessed.

Cycle 1 is defined as the initial 12 weeks of treatment periods, during which the three options are each assessed at a 4-week period (Figure 3). At the clinic visit marking the end of cycle 1, the patient and physician will discuss the comparative effectiveness and self-reported tolerability (specifically screening by cardiovascular, renal and gastrointestinal Review of Symptoms) of each of the tested options. Patients and Investigators will be blinded to reduce potential biases regarding different treatments. The drug that produces either an unacceptable side effect or the smallest decrease in disease activity will be removed from consideration. The remaining two drugs will be repeated for 4-week treatments (Cycle 2) in random order to confirm which drug yields the >reduction in disease activity without unacceptable side effects. We will repeat Cycle 2 if drugs cannot be differentiated.

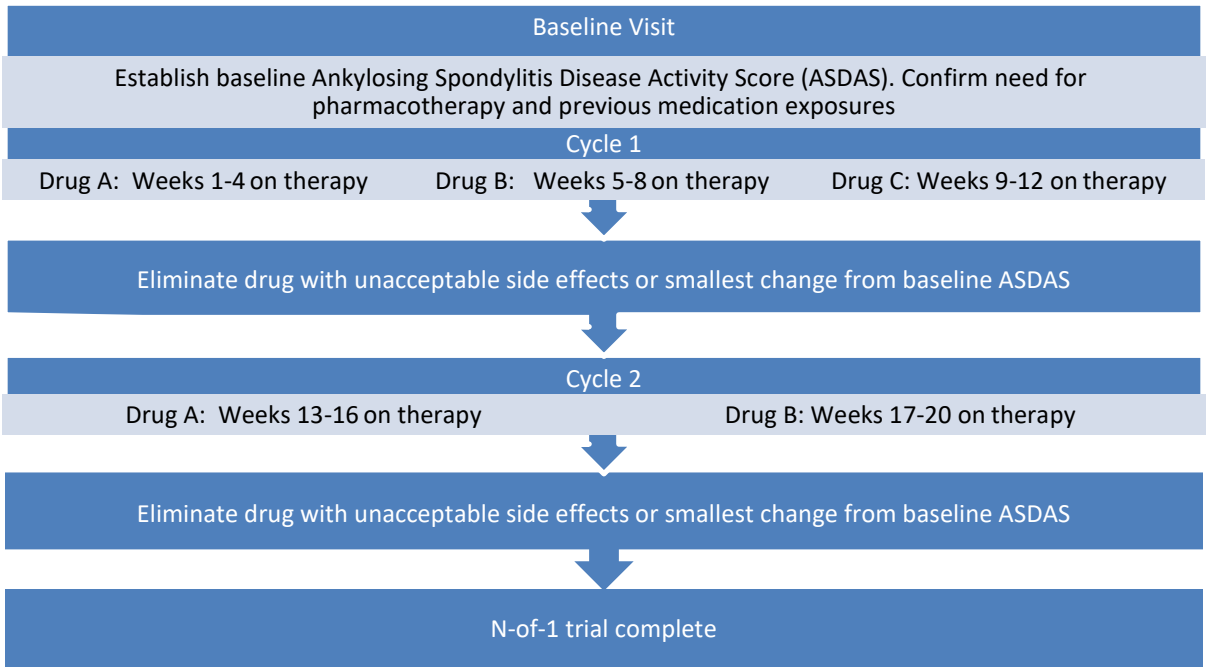

Figure 3. N-of-1 clinical trial schema

We will collect baseline serum samples in AxSpA patients (N=50). Olink® **proteomics use** DNA-coupled methods, (paired oligonucleotide binding) of antibodies with unique DNA reports (n=92) allow scaled multiplexing of candidate proteins. We will test the olink inflammation panel of 92 candidate proteins previously indicated in 45 inflammatory diseases. The performance of all tested proteins will be compared to current laboratory yardsticks (e.g. CRP). All candidate proteins will be tested in univariate modeling with student's t-test to look for differences between responders and non-responders. Non-normal data distributions will under log-transformation for comparisons.

5. SAFETY MEASUREMENTS

NSAIDs are FDA approved for various forms of arthritis and chronic pain, They are known disease-modifying drugs in AS. Adverse gastrointestinal events have been noted in clinical trials and post-marketing data including gastritis, bleeding, ulceration and perforation. Rofecoxib, a COX- 2 inhibitor, previously marketed under the label of Vioxx™ was pulled from the market by the FDA in 2004 due to increased cardiac events including myocardial infarction. A recent clinical trial comparing low dose celecoxib compared to moderate dose naproxen and ibuprofen did not demonstrate increased vascular suggesting this may not be a unique risk with selective NSAIDs (36). Thus, subjects are not exposed to any additional exposures when compared to routine care.

6. DATA ANALYSIS

All data will be collected utilizing a standardized case report form and entered into a REDCap™ database. Each subject will be assigned a study-specific number. Patients will be randomly assigned and data will be directly inputted by patients into the REDCap collected from standard AS-specific Patient Reported Outcome questionnaires with clinic-use-only touchpads.

Data collected will include: demographics, disease duration, laboratory values, and patient-reported outcome/quality of life questionnaires completed at the time of enrollment and up to one year post enrollment. Study coordinators will check for completeness of patient forms at the time of their visits. Each item inputted directly to REDCap will have validity checks performed to ensure data entered are accurate and that items are not skipped during entry by mistakes by the investigator team.

Any data that is deemed "missing" will be dropped from the study unless patients are re-contacted for adjuration within 24 hours by the study coordinators. A sensitivity analysis will be performed including those that were potentially dropped due to missing data

7. SAMPLE SIZE AND STATISTICAL METHODS

The data analytic strategy will use generalized linear multilevel modeling to account for clustering of participants with repeated observations. Modeling will use R v. 3.4 and Stan v. 1.10.(28, 29) Initial analyses examining group differences for baseline variables will use cross-tabulation, ANOVA's, and examination of correlations between baseline variables and specified outcomes. For the purposes of evaluating the comparability of groups, a posterior probability of $\geq$ 95% will constitute evidence for statistically reliable differences. Baseline or demographic variables on which group differences are detected, and which are correlated with outcomes, meet the definition of confounders (30) and will result in two sets of analyses: one in which the relevant variable is included as a covariate and one in which it is not. This will permit determination of the degree to which any group differences might confound conclusions regarding treatment. All analyses will be conducted on an intention-to-treat basis. Bayesian approaches will implement joint modeling of observed outcomes and missing data, which is robust to ignorable missingness (i.e., MCAR and MAR) (31). Sensitivity analyses will evaluate robustness of analytic conclusions to missing

data. Non-ignorable missing data patterns will be addressed through pattern-mixture modeling methods (32). Convergence of Bayesian analyses on the posterior distributions via Monte-Carlo Markov chain (MCMC) will be assessed via graphical (Gelman-Rubin Plots) and quantitative (Gelman-Rubin Diagnostics and Effective Sample Size) evidence. Evaluation of posterior distributions will permit statements regarding the probability that effects of varying magnitudes exist, given the data. Specification of diffuse, neutral priors will reflect the initial uncertainty regarding effect sizes. For all generalized linear multilevel models, priors for regression coefficients will be specified as ~Normal (μ=0, σ^2=100) on the identity or log-scale depending upon the model, level one error variances will be specified as ~Half-T (df = 3, mean = 0, standard deviation = 100). Prior distributions for level two variances will use ~Half-T (df = 3, mean = 0, standard deviation = 100). Priors for the comparison of proportions will be specified as ~Beta (α=0.5, β=0.5). To the degree possible we will also evaluate informative priors based on the previous literature data. Pre-specified post-hoc sub-group analyses will include comparing patients with: baseline high disease activity, modified New York Criteria for AS.

8. ETHICAL CONSIDERATIONS

Risks to Subjects

NSAIDs are FDA approved for various forms of arthritis and chronic pain, They are known disease-modifying drugs in AS. Adverse gastrointestinal events have been noted in clinical trials and post-marketing data including gastritis, bleeding, ulceration and perforation. Rofecoxib, a COX- 2 inhibitor, previously marketed under the label of Vioxx™ was pulled from the market by the FDA in 2004 due to increased cardiac events including myocardial infarction. A recent clinical trial comparing low dose celecoxib compared to moderate dose naproxen and ibuprofen did not demonstrate increased vascular suggesting this may not be a unique risk with selective NSAIDs (36). Thus, subjects are not exposed to any additional exposures when compared to routine care.

Protection against risks

The two main complications associated with NSAIDs are cardiac events and gastrointestinal bleeding. These estimates are unknown this patient population in part from the juxtaposed concepts of inflammation reduction leading to less cardiac events in rheumatic diseases vs. coronary vasospasm from COX inhibition with retrospective, observation studies conflicting in directionality of events. COX-2 inhibitors are thought to have less gastrointestinal events than nonselective NSAIDs.

9. PUBLICATIONS

We believe these studies will be impactful and of high interest to AxSpA patients and rheumatologists. We will submit our findings for presentation at planned international rheumatology meetings of SPARTAN, ACR and EULAR. We will plan to submit manuscripts to rheumatology journals ensuring dissemination of the work planned.